I. AMENDMENT

In the Claims:

Please delete claims 11 and 38, without prejudice or disclaimer.

Please amend the claims as follows:

1. (Amended three times) A method of reducing the growth rate of a tumor, comprising contacting a cell within said tumor (a) a DNA segment encoding a functional p53 protein and (b) a DNA damaging agent in a combined amount effective to inhibit the growth of said tumor, wherein functional p53 protein is expressed in the cell.

2. (Amended three times) The method of claim 1, wherein the DNA damaging agent is X-ray radiation, UV-irradiation, γ-irradiation, microwaves, adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mitomycin C, or cisplatin.

3. (Amended twice) The method of claim 2, wherein said cell is contacted with the DNA segment in combination with cisplatin.

4. (Amended three times) The method of claim 1, wherein the DNA segment is in a recombinant vector that expresses the functional p53 protein in said cell.

5. (Amended four times) The method of claim 4, wherein said p53-expressing recombinant vector is a naked DNA plasmid, a plasmid within a liposome, a retroviral vector, an AAV vector, or a recombinant adenoviral vector.

8. (Amended three times) The method of claim 4, wherein said recombinant vector comprises a p53 expression region, a cytomegalovirus IE promoter and an SV40 early polyadenylation signal.

9. (Amended) The method of claim 6, wherein at least one gene essential for adenovirus replication is deleted from said adenovirus vector and a p53 expression region is introduced in its place.

F2 cont'd 10. (Amended) The method of claim 9, wherein E1A and E1B regions of the adenovirus vector are deleted and the p53 expression region is introduced in their place.

~~12.~~ 11 (Amended twice) The method of claim 1, wherein said cell is first contacted with the DNA segment and is subsequently contacted with said DNA damaging agent.

F3

~~13.~~ 12 (Amended twice) The method of claim 1, wherein said cell is first contacted with said DNA damaging agent and is subsequently contacted with the DNA segment.

~~14.~~ 13 (Amended twice) The method of claim 1, wherein said cell is simultaneously contacted with the DNA segment and said DNA damaging agent.

~~15.~~ 14 (Amended twice) The method of claim 1, wherein said cell is contacted with a first composition comprising the DNA segment and a second composition comprising said DNA damaging agent.

F4

~~17.~~ 16 (Amended twice) The method of claim 1, wherein said cell is contacted with a single composition comprising the DNA segment in combination with said DNA damaging agent.

F5

~~22.~~ 20 (Amended three times) The method of claim 1, wherein said cell is a malignant cell.

F6

~~26.~~ 24 (Amended four times) The method of claim 1, wherein said cell is located within an animal at a tumor site.

F7

32. (Amended twice) A composition comprising a) an exogenous DNA segment encoding a functional p53 polypeptide and b) a DNA damaging agent.

SUB G2

~~33.~~ 26 (Amended three times) The composition of claim ~~32~~ 25, wherein the DNA damaging agent is adriamycin, 5-fluorouracil, etoposide, camptothecin, actinomycin-D, mitomycin C, or cisplatin.

F7 cont. ~~34.~~ 27 (Amended twice) The composition of claim ~~33~~ 26, wherein the DNA damaging agent is cisplatin.

~~35.~~ 28 (Amended twice) The composition of claim ~~32~~ 25, wherein the exogenous DNA segment is in a recombinant vector that expresses a functional p53 protein in an animal cell.

F8 ~~39.~~ 31 (Amended) The composition of claim ~~37~~ 30, wherein the recombinant vector is a recombinant adenoviral vector and the DNA damaging agent is cisplatin.

F9 ~~45.~~ 37 (Amended) The kit of claim ~~42~~ 34, wherein the recombinant vector is an adenovirus vector and the DNA damaging agent is cisplatin.

~~46.~~ 38 (Amended twice) The method of claim 1, wherein the cell is contacted with a DNA damaging agent by irradiating the cell with X-ray radiation, UV-irradiation, γ-irradiation or microwaves.

~~47.~~ 39 (Amended) The method of claim ~~46~~ 38, wherein the cell is contacted with a DNA damaging agent by irradiating the cell with X-ray radiation.

~~48.~~ 40 (Amended) The method of claim ~~46~~ 38, wherein the cell is contacted with a DNA damaging agent by irradiating the cell with UV-irradiation.

~~49.~~ 41 (Amended) The method of claim ~~46~~ 38, wherein the cell is contacted with a DNA damaging agent by irradiating the cell with γ-irradiation.

~~50.~~ 42 (Amended) The method of claim ~~46~~ 38, wherein the cell is contacted with a DNA damaging agent by irradiating the cell with microwaves.

F9 cont'd

~~51.~~ 43 (Amended twice) The method claim 1, wherein the tumor cell is contacted with a pharmaceutical composition comprising the DNA damaging agent.

F10

~~77.~~ 54 (Amended twice) The method of claim 4, wherein said DNA segment is administered prior to said DNA damaging agent.

~~78.~~ 55 (Amended twice) The method of claim 4, wherein said DNA segment is administered after said DNA damaging agent.

~~79.~~ 56 (Amended twice) The method of claim 4, wherein said DNA segment is administered at the same time as said DNA damaging agent.

F11

~~83.~~ 57 (Amended three times) The method of claim ~~26~~ 24, wherein said DNA segment is delivered to said tumor endoscopically, intravenously, intratracheally, intralesionally, percutaneously or subcutaneously.

F12

~~86.~~ 60 (Amended twice) The method of claim ~~13~~ 12, wherein there is 12 to 24 hours between administration of the DNA damaging agent and administration of the DNA segment.

~~87.~~ 61 (Amended twice) The method of claim ~~13~~ 12, wherein there is 6 to 12 hours between administration of the DNA damaging agent and administration of the DNA segment.

~~88.~~ 62 (Amended twice) The method of claim ~~13~~ 12, wherein there is about 12 hours between administration of the DNA damaging agent and administration of the DNA segment.

~~89.~~ 63 (Amended twice) The method of claim ~~12~~ 11, wherein there is 12 to 24 hours between administration of the DNA segment and administration of the DNA damaging agent.

~~90.~~ 64 (Amended three times) The method of claim ~~12~~ 11, wherein there is 6 to 12 hours between administration of the DNA segment and administration of the DNA damaging agent.

F12 cont. 65

(Amended three times) The method of claim ~~12~~ 11, wherein there is about 12 hours between administration of the DNA segment and administration of the DNA damaging agent.

F13 ~~101~~ 71. (Amended) The method of claim ~~23~~ 21, wherein said lung cancer cell is a small cell lung carcinoma cell.

F14 ~~119~~ 78. (Amended) The method of claim ~~47~~ 39, wherein the cell is irradiated with about 2000 to 6000 roentgens.

~~120~~ 79. (Amended) The method of claim ~~47~~ 39, wherein the cell is irradiated with about 50 to 200 roentgens.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

In the Office Action dated November 16, 2001, claims 1-20, 22-26, 32-61, 77-79, 83-91, 96-101, 111, 112, 115-120, and 128-130 were rejected. Herein, claims 11 and 38 are cancelled. Claims 1-5, 8-10, 12-15, 17, 22, 26, 32-35, 39, 45-51, 77-79, 83, 86-91, 101, and 119-120 are amended. Support for the Amended claims can be found in the Specification at least on page 2, line 18-20; page 9, lines 5-12; page 10, lines 10-13,; and in the originally filed claims . These cited passages and the use of a vector to deliver p53 to a cell provide support for the term "exogenous DNA segment," as an endogenous nucleic acid does not require delivery to a cell. *See e.g.,* specification at page 9, lines 5-10 and page 10, lines 10-12. Thus, no new matter is being added. A copy of the claims as amended is shown in Appendix A. A copy of the pending claims is shown in Appendix B for the Examiner's convenience.

B. Information Disclosure Statement is Proper

The Action indicates that the Information Disclosure Statement (IDS) filed on April 24, 2001 fails to comply with 37 C.F.R.§1.98(a)(3) because a citation was not accompanied by any comment or discussion concerning the relevancy of the patents in printed publications. The Action further contends that the IDS has been placed in the Application File but the information referred to therein has not been considered. Applicants urge that this action is not proper, and requests that the Information Disclosure Statement be properly considered. According to 37 C.F.R. §1.98(a)(3), a concise explanation of the relevance is required "of each patent, publication, or other information listed *that is not in the English language*." The 96 references on the IDS submitted on April 24, 2001 do not fall within this Section. As such, a statement regarding their relevance is not necessary or required. Applicants provide a copy of the filed IDS and look forward to receiving it with the Examiner's initials next to each reference.

C. Double-Patenting Rejections Will be Overcome

1. Rejection over U.S. Patent No. 5,747,469

The Action rejects claims 1-20, 22-26, 46-61, 77-79, 83-91, 96-101, 111-120, and 127-130, under the judicially created doctrine of Obviousness-Type Double Patenting, as being unpatentable over claims 1-105 of U.S. Patent No. 5,747,469. Applicants submit herewith a terminal disclaimer to overcome this rejection. (Appendix C).

2. Rejection of claims over U.S. Patent No. 6,069,134

The Action rejects claims 1-20, 22-26, 46-61, 77-79, 83-91, 96-101, 111-120, and 127-130 under the judicially created doctrine of Obviousness-Type Double Patenting over claims 1-69 of U.S. Patent No. 6,069,134. Applicants submit herewith a terminal disclaimer over the cited patent (Appendix D).

D. Claim Objections

The Action objects to claim 38 for reciting "said recombinant vector." This claim has been amended to delete "is a recombinant adenoviral vector." Claim 38 and claim 11 has been cancelled to reflect that an "adenoviral vector" is used synonymously with an "adenovirus." *See e.g.*, specification at page 44, lines 9-12 and Examples 1 and 2.

The Action also objects to claim 101 as depending from canceled claim 95. Claim 101 has been amended to depend from claim 23.

E. The Claims Are Enabled

The Action rejects claims 1-20, 22-26, 46-61, 77-79, 83-91, 96-101, 111, 112, 115-120, and 128-130 under 35 U.S.C. §112, first paragraph, because the specification allegedly fails to reasonably provide enablement for a method of reducing the growth rate of a tumor by introducing any p53-expressing gene that encodes a functional p53 protein into a tumor, while exposing the tumor to a DNA-damaging agent in a non-mouse model animal. The Action admits that the specification is enabling for a method of reducing the growth rate of a tumor by introduction of a gene-encoding a wild-type p53 protein in a mouse model. The Action further contends that the working examples provided used a wild-type p53 gene, which expresses a wild-type p53 protein, and only limited prophetic guidance. Furthermore, the Action argues that the only working example provided is in a mouse model system, and the alleged limited prophetic guidance does not provide a nexus between the mouse model system and any other animal. The Action argues that gene therapy is problematic, citing various references, including Verma *et al.*, Orkin *et al.*, and Anderson. The reference of Levine is said to show that the state of the art at the time of the filing of this Application was "still developing" and that no prior art teachings would instruct one with skill in the art how to make or use any non-wild type p53

expressing gene in the instant method. The action concludes that, "A skilled artisan would need to have practiced considerable, non-routine trial and error experimentation to enable the full scope of the claims." Applicants respectfully traverse this rejection.

1. Applicants have already responded to and overcome this rejection

In the Office Action dated March 15, 1999—more than *two years* before the present Action—an enablement rejection was made based on the same references cited in the current Action. Orkin, Verma *et al.*, and Anderson were cited in the March 15, 1999 Office Action for support for the contention about the state of the art and the prior art at the time of the invention. Applicants responded to that rejection in a response filed on August 27, 1999:

> First, applicants object to the rejection on the grounds that the parent application, which has issued as U.S. Patent 5,747,469, has effectively disposed on these issues. The examiner has not pointed to any difference between the claims of the present application, and those of the parent, that would alter the enablement analysis. Thus, applicants submit that the issue of enablement is *res judicata* against the PTO by virtue of the issuance of U.S. Patent 5, 747,469.
>
> Second, in contrast to the examiner's argument, gene therapy is not an unproved endeavor. Attached to this response are declarations from Dr. Jack Roth, submitted during the prosecution of U.S. Patent 5,747,469. These declarations provide specific evidence of (a) a p53 gene therapy's effectiveness generally, and (b) specific successes using a combination of p53 gene therapy and DNA damaging agents. These declarations effectively rebut the examiner's unsubstantiated allegations regarding gene therapy.
>
> And third, applicants dispute the examiner's analysis of the *Wand*'s factors. It is absolutely untrue that the instant specification provides guidance only for *in vitro* practice of the invention. In making this statement the examiner ignores a considerable portion of the specification, for example, pages 40-43 specifically contemplate and discuss therapeutic protocols. Moreover, methods and compositions for *in vivo* gene transfer and delivery of pharmaceutical agents also are described. For example, pages 30-34 describe the use of viral vectors to deliver therapeutic genes *in vivo*. Furthermore, starting at page 63, there is both a discussion of *in vivo* animal studies, and a description of a putative clinical protocol. Thus, there is no basis in the examiner's assertion that specification does not address *in vivo* embodiments.

Regarding the nature of the invention, the prior art, and the state of the art, while clearly evincing the complexities involved with gene therapy, do not suggest a lack of enablement. To the contrary, all of the limitations discussed by the examiner indicate that, while far from perfect, gene therapy is a viable endeavor. 35 U.S.C. §112, first paragraph does not require that the invention be free from limitations, only that it can be practiced by one of ordinary skill in the art.

Applicants also submit that though some experimentation may be required to apply the invention to particular clinical situations, that experimentation would not be considered undue, especially in light of the fact that considerable experimentation is considered routine in the field.

In light of the preceding comments, applicants respectfully request that the examiner reconsider and withdraw the rejection.

In the subsequent Office Action, mailed November 22, 1999, the Office Action states, "Applicant's rebuttal regarding the rejection of . . . claims 1-26, 32-61, 77-79, 83-89, 96-101, 111-112, 115-120 and 127-130 under 35 U.S.C. 112, first paragraph is found *convincing* and the rejection is *withdrawn*." Page 2 (emphasis added). In no way does the present Action indicate the difference between the previously withdrawn rejection and the present rejection. Applicants contend an enablement rejection based on the references of Orkin, Verma *et al.*, and Anderson has already been overcome. Applicants submit as Appendix E a copy of the declarations of Jack Roth that were submitted as part of a response to the previous enablement rejection. Furthermore, Applicants provide additional basis to support the withdrawal of the enablement rejection.

2. The references cited in the Action are irrelevant to the claims

The Action cites the references of Orkin, Anderson, and Verma *et al.* to show that gene therapy is generally unpredictable. Applicants emphasize that those references do not address **p53** gene therapy as recited in the claims, and instead, generalize about gene therapy. Furthermore, none of these articles state that gene therapy will not work and is a complete

failure. Instead, they focus on more clinical issues, which are above and beyond the standards for patentability. *See In re Krimmel*, 292 F.2d 948, 954 (C.C.P.A. 1961) ("There is nothing in the patent statute or any other statutes . . .which gives the Patent Office the right or the duty to require an applicant to prove that compounds or other materials which he is claiming, and which he has stated are useful for 'pharmaceutical applications,' are safe, effective, and reliable for use with humans."). Proof of efficacy in clinical trials involving humans is not a requirement for patentability. *See In re Brana,* 51 F.3d 1560 (Fed. Cir. 1995).

Anderson, *Nature* 392:25-30, 1998, reviews gene therapy and *merely speculates* that "immunogenicity, stability of gene expression, and persistence *in vivo*" may differ with respect to the "exact vector design, the tissue type that the vector is introduced into, and the nature of the transgene insert." This statement does not indicate that the therapy recited by the claims will not be effected, particularly since the transgene insert in this case—p53—is a limitation of the claim. Moreover, this reference does not discuss Ad-p53, the subject matter of the invention. That there is unpredictability in the field of Ad-p53 gene therapy, especially since the specification teaches that Ad-p53 gene therapy works, cannot be gleaned from the Anderson reference.

Similarly, the text of the Verma reference, *Nature* 389:239-242 makes no comment about Ad-p53 cancer therapy that would suggest the claims are not enabled. Applicants emphasize that the claims are directed to Ad-p53 cancer therapy, which the specification teaches, and this reference does not indict the disclosure in any way. For example, the reference does not say that practicing Ad-p53 cancer therapy according to the claims would require undue experimentation. Applicants contend that that the Verma reference is not dispositive on the issue of enablement.

The Orkin reference is cited by the Action as showing that the prior art indicates that there are problems in the field of gene therapy. Applicants contend that the state of the prior art

is irrelevant in light of the fact that the specification of the invention provides *in vivo* data in a mouse showing a "method of reducing the growth rate of a tumor" with a functional p53 and a DNA damaging agent.

Furthermore, the citation to the Levine reference is also not relevant. The claims are directed to the use of a "DNA segment encoding a functional p53 polypeptide." There is nothing in the Levine reference that indicates such a segment would not work as described in the specification or that undue experimentation would be required to practice the invention.

3. The specification provides ample direction to practice the claimed invention

"The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" MPEP 2164.08 (citing *In re Wright*, 999 F.2d 1557, 1561, 27 U.S.P.Q. 1510, 1513 (Fed. Cir. 1993)). With respect to this rejection, the claimed invention is generally directed to "A method of reducing the growth rate of a tumor, comprising contacting a cell within said tumor with (a) a gene encoding a functional p53 protein and (b) a DNA damaging agent in a combined amount effective to inhibit the growth of said tumor." Claim 1. The specification clearly teaches how to practice the claimed invention. Examples 7 and 8 show that the combination of CDDP and Ad-p53 induced apoptosis in cancer cells *in vitro* and *in vivo*.

Applicants respectfully note that "it is incumbent upon the Patent Office...to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.05 (quoting *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (CCPA 1971)). As was discussed above, none of the references cited in the Action cast doubt as to the sufficiency of the present disclosure to allow a person of ordinary

skill in the art to practice the invention without undue experimentation. There is no reason provided why a person could not take the disclosure and practice the invention as claimed. Accordingly, the specification teaches how to make and use the claimed invention, and thus, it enables the claimed invention.

4. Declaration of Deborah R. Wilson rebuts argument about gene therapy

Applicants submit the declaration of Deborah R. Wilson, the Associate Vice President of Clinical Research at Introgen Therapeutics ("Introgen") as evidence to rebut the examiner's contention about gene therapy that provide the basis for rejecting the claims as not enabled (Appendix F).[1] Dr. Wilson's declaration sets forth the numerous clinical trials with Ad-p53, including Introgen's INGN 201 adenovirus-p53 composition, which is disclosed in the specification of the present application. These trials are underway, have recently been completed, or have already been approved. They involve the use of the Ad-p53 composition alone and in combination with a DNA damaging agent. The declaration also sets forth a number of clinical trials that have employed another Ad-p53 construct, Schering Plough's SCH 58500 construct. Thus, this declaration provides evidence to rebut the examiner's contentions regarding gene therapy and eliminates any doubts as to the operability and efficacy of a combination treatment.

Applicants point to M.P.E.P., albeit on the subject of utility instead of enablement, which states, "[A]s a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." M.P.E.P. § 2107.03 ("IV. Human Clinical Data"). Because the requirements for utility and

[1] Copy of assigned declaration is provided. Th

enablement are intertwined, Applicants contend that the submission of bountiful clinical trial evidence strongly weighs against a rejection for enablement. The clinical trial evidence shows that adenovirus-p53 is being tested against a number of cancers, including head and neck, non-small cell lung carcinoma, ovarian, breast, esophageal, lung, glioma, prostate, bladder, and solid tumors from colon cancer, breast cancer, prostate cancer, sarcomas, non-small cell lung carcinomas, and head and neck cancer.

The Declaration of Deborah R. Wilson rebuts the examiner's contentions about gene therapy. As such, there is no basis to assert the claimed invention is not enabled. Accordingly, Applicants respectfully request the rejection of all the claims for lack of enablement be withdrawn in view of the foregoing reasons.

F. The Claims Are Definite

The Action rejects claims 1-20, 22-26, 32-61, 77-79, 83-91, 111, 112, 115-120, and 128-130 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as their invention. The individual rejections are discussed below.

1. Claim 1 is amended

The Action rejects claim 1 as being incomplete for omitting essential steps. The omitted step is said to be providing for the expression of the p53 gene. Applicants amend claim 1 to recite, "wherein functional p53 protein is expressed in the cell."

2. Claim 2 is amended

Claims 2-3, 33, 34, and 39 are rejected as allegedly having no clear nexus between the "DNA damaging agent" of claim 1 and the list provided in claim 2. Claim 2 is amended to recite "wherein the DNA damaging agent is" and is followed by the list of agents.

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e originally assigned declaration will be submitted shortly.

3. Claim 4 is amended

Claim 4 is said to be vague because it recites a recombinant vector that expresses a functional p53 protein in a cell, yet depends from Claim 1, which recites a gene-encoding of a functional p53 protein. Claim 4 has been amended to clarify the invention. It now recites, "wherein the DNA segment is in a recombinant vector that expresses the functional p53 protein in said cell."

4. Rejection is rendered moot

The Action rejects claims 4-11, 19, 20, 25, 33-39, 77-79, 128-130, as unclear because claim 4 recites a recombinant factor that expresses a functional p53 protein. It is alleged that there is no linking language to relate that to the "p53 gene" of independent claim 1. The amendment discussed above renders this rejection moot.

5. There is no antecedent basis problem with claim 5

Claim 5 is said to lack antecedent basis for the limitation "said p53-expressing recombinant." Applicants traverse this rejection. Claim 5 recites "said p53 expressing recombinant vector" and claim 4 recites "a recombinant vector that expresses the functional p53 protein." A person of ordinary skill in the art would understand that claim 4's limitation provides antecedent basis for the limitation in claim 5. Accordingly, as there is no requirement that the language from the two claims be exact, claim 5 is definite.

6. Claim 5 is amended

The use of "or" in two locations of claim 5 is said to render claim 5 ambiguous as to what is being claimed. The first "or" has been deleted in the amended claim.

7. There is no antecedent basis problem with claims 6 and 7

The Action rejects claims 6 and 7 for lacking antecedent basis for "said p53-expressing recombinant." For the reasons discussed above, there is no antecedent basis problem with "said p53-expressing recombinant vector" because claim 4 recites "a recombinant vector that expresses the functional p53 protein."

8. Claim 8 is amended

Claim 8 is rejected as lacking antecedent basis for a limitation, "the cytomegalovirus," and the "SV40" early polyadenylation signal. Applicants have amended claim 8 to recite "a cytomegalovirus IE promoter" and "an SV40 early polyadenylation signal."

9. Claims 9 and 10 are amended

Claims 9 and 10 are rejected for the limitation, "The p53 expression region," as lacking antecedent basis. Claim 10 is further rejected for the limitation "the E1A and E1B regions." Claims 9 and 10 are amended to eliminate these issues.

10 Claims 11, 38, 39, and 49 are amended or cancelled

Claims 11, 38, 39, and 49 recite the limitation, "a recombinant adenoviral vector is present within a recombinant adenovirus," which is said to be unclear. Applicants have cancelled claims 11 and 38 and amended claims 49 and 45 to clarify the invention.

11. Claims 22 and 26 are amended

The Action rejects claims 22 and 26 for lacking sufficient antecedent basis for the limitation "said tumor cell." Claims 22 and 26 have been amended to recite "the cell."

12. Claims 11, 38, 39, and 49 are amended or cancelled

Claims 51-61 and 115-118 are said to be unclear because claim 51 recites a "DNA damaging compound," while claim 1, from which claims 51 depends, recites "DNA damaging agent." Claim 51 has been amended to recite "DNA damaging agent."

13. Claims 86-91 are amended

Claims 86-91 are said to lack antecedent basis for "the period." Applicants have amended claims 86-91 to address this issue, although Applicants believe a person of ordinary skill in the art would understand the claims with reasonable certainty, as is required for compliance with 35 U.S.C. § 112, second paragraph.

14. Claims 86-91 are amended

Claim 101 is rejected for the limitation, "said lung cancer cell is a small cell lung carcinoma cell, because it depends from claim 97, which recites, 'said lung cancer cell is a non-small-cell lung carcinoma cell.'" Claim 101 has been amended to depend from claim 23.

15. Claims 119 and 120 are amended

Claims 119 and 120 are rejected for the limitation, "the x-ray dosage," as lacking sufficient antecedent basis. Applicants have amended claims 119 and 120.

F. Claim 32 Is Not Anticipated by the Cited References

1. Tishler *et al.* does not anticipate claim 32

The Action rejects claim 32 under 35 U.S.C. §102(a) as being anticipated by Tishler *et al.* ("Tishler"). Tishler is said to teach a composition comprising a gene encoding a functional p53, in combination with the DNA damaging agent. Applicants respectfully traverse this rejection.

Claim 32 recites a "composition comprising an exogenous DNA segment encoding a functional p53 polypeptide in combination with a DNA damaging agent." Tishler does not teach

an "exogenous DNA segment encoding a functional p53 polypeptide" Instead, the experiments discussed in Tishler involved endogenous p53. *See, e.g.,* Tishler at page 2213 ("Fig. 1A illustrates EMSA binding of endogenous wt*p53*....). "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Furthermore, it does not discuss or suggest any cancer treatments or the use of an exogenous DNA segment encoding a functional p53 polypeptide. It states merely that the authors "assessed how DNA damaging agents altered the levels of wt*p53*-DNA binding" and concludes that the "data indicate that DNA strand breaks may be sufficient to cause increases in *p53* binding activity." In no way does this reference teach or even suggest all of the elements of the claimed invention.

Because Tishler concerns endogenous p53, it cannot meet the limitation of an "exogenous DNA segment"; consequently, it does not teach an element of claim 32, and it cannot anticipate the claimed invention. Applicants respectfully request this rejection be withdrawn.

2. Claim 32 is not anticipated by Clarke *et al.*

The Action rejects claim 32 as being anticipated under 35 U.S.C. §102(a) by Clarke *et al.* ("Clarke"). Clarke is said to teach a composition comprising a gene encoding a functional p53 polypeptide in combination with the DNA damaging agent. Applicants respectfully traverse this rejection.

Like the Tishler reference, Clarke also does not anticipate the claimed invention because it does not teach an "exogenous DNA segment encoding a functional p53 polypeptide." In fact, the experiments disclosed in Clarke involved inactivating one or more endogenous p53 genes by

introducing a deletion. Clarke does not meet the limitation of an "exogenous DNA segment encoding a functional p53 polypeptide." This is not surprising because Clarke is not investigating the effects of p53 and chemotherapy or radiation on cells; instead, Clarke is studying the induction of apoptosis in thymocytes lacking p53. Therefore, it does not anticipate the composition of claim 32. Applicants respectfully request this rejection be withdrawn.

3. Claim 32 is not anticipated by Lane

The Action rejects claim 32 under 35 U.S.C. §102(b) as being anticipated by Lane. Lane is said to teach a composition comprising a gene encoding a functional p53 polypeptide in combination with a DNA damaging agent. Applicants respectfully traverse this rejection.

It is not clear what portion of Lane is being relied upon as teaching the claimed invention. While Lane does disclose some experiments of others in which "treatment of cells with ultraviolet light or radiomimetic drugs induced the accumulation of normal p53 through a posttranslational stabilization mechanism" (page 16), there is no description in Lane, however, of a composition comprising an "exogenous DNA segment encoding a functional p53 polypeptide" alone or in combination with a DNA damaging agent. Thus, it does not meet the limitations of claim 32. As such, it does not anticipate the claim. Applicants respectfully request this rejection be withdrawn.

H. The Claims Are Not Obvious

The Manual of Patent Examining Procedure (MPEP) sets forth three basic criteria that must be met to establish a *prima facie* case of obviousness:

(1) "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings";

(2) "there must be a reasonable expectation of success"; and

(3) "the prior art reference (or references when combined) must teach or suggest all the claim limitations."
MPEP §2142.

The Action issues several obviousness rejections against the claims, which are all defective. None of the rejections satisfies all three requirements, and accordingly, they should be withdrawn.

1. Claims 32-36 and 39-41 are non-obvious over Lane in view of Tishler, Kastin *et al.*, and Kuerbitz *et al.*

The Action rejects claims 32-36 and 39-41 under 35 U.S.C. §103(a) as being unpatentable over Lane in view of Tishler, Kastan *et al.* ("Kastan"), and Kuerbitz *et al.* ("Kuerbitz"). Lane is said to teach a composition comprising a gene encoding of functional p53 polypeptide, in combination with the DNA damaging agent. The Action concedes Lane does not teach that the gene encoding of functional p53 polypeptide was contained in a plasmid, nor did Lane teach that the DNA damaging agent was a compound listed in claim 33. Tishler is said to teach the expression of p53 polypeptide in combination with the list of DNA damaging agents. Kuerbitz is said to teach a composition comprising a gene encoding a functional p53 polypeptide, in combination with the DNA damaging agent, where the p53 gene is in a plasmid that was introduced into target cells along with the DNA damaging agent.

Finally, Kastan is said to teach a composition comprising a gene encoding a functional p53 polypeptide in combination with the DNA damaging agent, and that the loss of wild-type p53 gene expression in a cell leads to cell proliferation in cells exposed to DNA damaging agents. The action contends it would have been obvious to one with ordinary skill in the art at the time of the filing of the invention to combine the teachings of Lane with the teachings of Tishler, Kastan and Kuerbitz because Lane taught the introduction of p53 expressing genes into

cells, and Lane taught the expression of p53 in a cell in combination with DNA damaging agents in a method to treat tumors by killing the cells of the tumors. The Action argues that one of ordinary skill in the art would have been motivated to combine the teachings, because each of them taught the advantageous and available use of the composition comprising a gene encoding of p53 polypeptide, in combination with DNA damaging agents, to kill tumor cells using the composition. The Action concludes that a person of ordinary skill in the art would have had a reasonable expectation of success in producing the instant invention given the teachings of the cited references. Applicants respectfully traverse this rejection.

a. The references do not teach what the examiner contends

Lane is said to teach a composition comprising a gene encoding of functional p53 polypeptide, in combination with the DNA damaging agent. Lane does not teach, however, an "exogenous DNA segment encoding a functional p53 polypeptide." Furthermore, it states that the "most appealing option" for treating cancer is "to induce p53 with a nontoxic agent to arrest the normal cells and then treat the tumour with a high dose of the conventional agent, thus radically increasing therapeutic effectiveness." Lane at page 16. Lane is referring to radiation and chemotherapy as the conventional agent. In no way does Lane suggest a composition comprising an "exogenous DNA segment encoding a functional p53 polypeptide." Lane contemplates inducing *endogenous* p53 in normal cells and treating the tumor cells with radiation or chemotherapy. It does not provide the teaching the Action contends. As a result, there is no basis for the rejection.

b. There is no motivation or suggestion to combine references

To render claims obvious, the cited references must suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed

process. *In re Vaeck*, 20 U.S.P.Q. 2d 1438, 1443 (Fed. Cir. 1991) *citing In re Dow Chemical Co.*, 5 U.S.P.Q. 2d 1529, 1531 (Fed. Cir. 1988). The cited references do not meet this criterion.

The Action contends that one of ordinary skill in the art would have been motivated to combine the teachings of Lane with the teachings of Tishler, Kastan, and Kuerbitz because each of them taught the advantageous and desirable use of a composition comprising an expressed gene encoding a p53 polypeptide in a cell in combination with a DNA damaging agent to kill cells of a tumor. That contention is inaccurate. None of them teaches the advantageous and desirable use because none of them concerned the administration of an DNA segment encoding a functional p53 polypeptide and a DNA damaging agent to cells of a tumor. The examiner makes an assumption that because the references make conclusions about p53 based on *endogenous* p53, it would have been obvious to administer *exogenous* p53 to cancer cells. However, none of these references state this or suggest this. "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination." MPEP § 2143.01 citing *In re Mills,* 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990) (emphasis added). In this case, the cited references do not suggest that they should be combined with one another. Instead, the Examiner is seeking to employ impermissible hindsight in reconstructing the elements necessary to achieve the invention piecemeal from the prior art. *See Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 873 (Fed.Cir.1985). The Federal Circuit has repeatedly held that such hindsight reconstruction is an improper basis for a §103 rejection. *See id.*

Furthermore, the reference of Lane, as discussed above, does not suggest or motivate the claimed invention. In fact, Lane *teaches away* from the claimed invention. Again, it says the best option for treating cancer is to induce wild-type p53 in normal cells and then treats cancer

cells with traditional cancer therapy, such as chemotherapy or radiation. Lane at page 16. "The relevant portions of a reference include not only those teachings which would suggest particular aspects of an invention to one having ordinary skill in the art, but also those teachings which would lead such a person away from the claimed invention." *In re Mercier,* 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975). Lane does not suggest administering an exogenous DNA segment encoding a functional p53 polypeptide to a cell within a tumor. It does not motivate combining the cited references with one another to produce the methods of the invention.

To summarize, the cited references do not teach, suggest or motivate the claimed invention, and instead, one of the references actually teaches away from the claimed invention. The examiner's *prima facie* obviousness rejection cannot stand, and Applicants respectfully request it be withdrawn.

c. No reasonable expectation of success

As required by the Federal Circuit and the MPEP, to render claims obvious, the cited references must reveal that in so making or carrying out, those of reasonable skill would have a reasonable expectation of success. *In re Vaeck*, 20 U.S.P.Q.2d at 1443. Because none of the references describes or divulges any data involving the claimed invention, a person of ordinary skill in the art would not have had a reasonable expectation of practicing the claimed invention. There is no reason based on any of the cited references that a method of treating cancer could be effected by administering to a cell within a tumor an exogenous DNA segment encoding a functional p53 polypeptide in combination with chemotherapy or radiation. The references simply do not address this situation. Thus, for this reason as well, the obviousness rejections based on these references are defective and should be withdrawn.

d. At best, cited references amount to an improper "obvious to try" situation

Even if the references provided the teachings the examiner erroneously accredits to them, they would constitute, at best, an improper "obvious to try" grounds for rejection. *See Jones v. Hardy,* 220 U.S.P.Q. 1021, 1026 (Fed. Cir. 1984). According to *In re Eli Lilly & Co.,* 14 U.S.P.Q.2d 1741, 1743 (Fed. Cir. 1990), "[a]n 'obvious to try' situation exists when...further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired result or indicate that the claimed result would be obtained if certain directions were pursued." The references of Lane, Tishler, Kastan, and Kuerbitz cannot provide the disclosure necessary to render the claimed invention obvious. For the foregoing reasons, Applicants respectfully request the rejections based on these references be withdrawn.

2. Claims 32-41 are non-obvious over Lane, Tishler, Kastan and Kuerbitz, and further in view of Bacchetti *et al.*

The Action rejects claims 32-41 under 35 U.S.C. §103(a) as being unpatentable over Lane, Tishler, Kastan and Kuerbitz, and further in view of Bacchetti *et al.* ("Bacchetti"). The Action admits that Tishler, Kastan and Kuerbitz do not teach that the gene encoding P53 is contained in an adenoviral vector. Bacchetti is said to teach the use of adenoviral vectors for the expression of a p53 gene. The Action contends it would have been obvious to one of ordinary skill in the art to combine the teachings of Lane, Tishler, Kastan and Kuerbitz with the teachings of Bacchetti because Bacchetti taught the advantageous and desirable use of an adenoviral factor, which expresses higher levels of p53 in a cell. It further argues that a person of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention given the teachings of the cited references. Applicants respectfully traverse this rejection.

For the reasons discussed in the previous section, the references of Lane, Tishler, Kastan, and Kuerbitz do not render obvious claims 32-36 and 39-41. The addition of Bacchetti does nothing to address the defect in the combination of references. Bachetti is cited as teaching only the advantageous and desirable use of an adenoviral vector. It does not remedy the lack of motivation or suggestion to combine the references of Lane, Tishler, Kastan, and Kuerbitz, nor does it indicate there would be a reasonable expectation of success at achieving the claimed invention. Consequently, claims 32-41 are not rendered obvious by the cited references. Applicants respectfully request this rejection be withdrawn.

3. Claims 32-41 are non-obvious over Lane, Tishler, Kastan, Kuerbitz, Bacchetti, and further in view of the Stratagene catalog

The Action rejects claims 32-41 under 35 U.S.C. §103(a) as being unpatentable over Lane, Tishler, Kastan, Kuerbitz, Bacchetti, and further in view of the Stratagene catalog. Lane, Tishler, Kastan, Kuerbitz and Bacchetti are admitted not to teach a kit containing the claimed compositions. However, the Action contends that the Stratagene catalog teaches "that kits have advantages for combining reagents for use in assays," and as such, a person of ordinary skill in the art would have been motivated to combine the teachings of the Stratagene catalog with the other cited teachings. Applicants respectfully traverse this rejection.

Again, for the reasons discussed above, the claimed invention is not rendered obvious by the combination of Lane, Tishler, Kastan and Kuerbitz. The addition of the Stratagene catalog to address the kit claims does not address the fundamental defect with the obviousness rejection of claims from which the kit claims depend. For this reason alone, the obviousness rejection fails.

Furthermore, there is simply no motivation or suggestion to combine *any* of the previously cited references with the Stratagene catalog. A *prima facie* case of obviousness requires this much. The Stratagene catalog does not provide even a single kit involving a

pharmaceutical composition for use in treating disease. Instead, it concerns reagents for scientific experiments—DNA and RNA Sequencing Kits, Exo/Mung Nuclease Detection Kit, RNA Transcription Kit, RNA Transcription Buffer Kit, mRNA Capping Kit, *In vitro* Express Translation Kit, and *pico*Blue Immunoscreening Kit. None of these is intended for use as a treatment or pharmaceutical composition. This reference simply does not concern the type of kits contemplated by the claimed invention. As such, it does not suggest or motivate a person of ordinary skill in the art to combine the cited references to produce the claimed invention. Applicants respectfully request this rejection be withdrawn.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,

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